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Case Report

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Successful treatment of concurrent acute migraine headache and atrial fibrillation with benzodiazepine administration

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ABSTRACT

Migraine and atrial fibrillation (AF) are common disorders in the general population in which autonomic nervous system takes role in the pathophysiological mechanism of both diseases. Migraine is a primary headache disease that is associated with significant debilitating symptoms and disability especially among young individuals and AF is associated with excess risk of morbidity and mortality. Interaction between migraine and AF has been a major interest since years at a pathophysiological and clinical level. Benzodiazepines (BZDs) are a class of psychotropic drugs that act through gamma amino butyric acid-A receptors located in the central nervous system. BZDs are widely used for their anxiolytic, anticonvulsant, sedative-hypnotic, and muscle relaxant effects. Herein, we describe a case of a patient presenting with concurrent acute migraine headache and AF attack and successful treatment of both conditions simultaneously with intravenous administration of BZD.

Keywords: Autonomic nervous system, atrial fibrillation, benzodiazepine, migraine.

INTRODUCTION

Migraine is a common primary headache disorder in which genetic and environmental components both involve in the pathogenesis. Characteristics of the disease include headache with repetitive, unilateral, and throbbing pattern usually accompanying photophobia and phonophobia. In addition, autonomic symptoms such as nausea, vomiting, flushing, lightheadedness, piloerection are common in migraine. Autonomic symptoms are mostly seen in migraine with aura and that paradoxical sympathetic hypersensitivity takes part during migraine attacks suggesting an important role for autonomic dysfunction in the pathophysiology.[1,2]

Atrial fibrillation (AF) is the most prevalent arrythmia type worldwide and associated with increased risk of morbidity and mortality. Akin to the migraine pathophysiology, alterations in autonomic nervous system functioning are the major drivers in AF pathogenesis.2,3 Therefore, interaction between migraine and AF has been a major interest since years at a pathophysiological and clinical level. Migraine is known to be a risk factor for AF development, but coexistence of AF and migraine headache has rarely been reported in the literature until now.[2,4,5]

Benzodiazepines (BZDs) are a class of psychotropic agents acting through gamma amino butyric acid (GABA)-A receptors which are ligand-gated and chloride-selective ion channels. Because BZDs reduce neuronal excitability, they are widely used in various neurologic and psychiatric conditions such as status epilepticus, anxiety, insomnia and delirium.[6] In this case report, we describe a case of a patient presenting with concurrent acute migraine headache and AF attack and successful treatment of both conditions simultaneously with intravenous (iv) administration of BZD.

CASE

A 47-year-old male patient with a history of migraine was admitted to our emergency department (ED) with the complaint of headache resulting with syncope. Initial evaluation revealed a heart rate of 100 beats per minute approximately and blood pressure of 110/70 mmHg. He had no fever and decreased oxygen saturation obtained from pulse oximetry. Neurological examination was normal and cardiac auscultation revealed irregular heart rate with no pathological sounds or murmurs. 12-lead electrocardiography obtained in the ED was consistent with AF accompanying high ventricular rate (**Figure 1**). Detailed anamnesis revealed no history of cardiac disease and risk factors except smoking. His headaches were very rare and associated with visual aura, irritability, and photophobia. However, he denied concomitance of syncope and/or palpitations during the previous attacks. He was on dexketoprofen treatment for

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migraine prophylaxis for years. Laboratory tests including cardiac enzymes, natriuretic peptide level and thyroid function tests were all within normal limits. Cranial computed tomography and diffusion magnetic resonance imaging were also normal. Transthoracic echocardiography demonstrated mild mitral and tricuspid regurgitation with slightly increased left atrium diameter. Dexketoprofen and metoprolol was applied to the patient respectively through iv route but neither AF nor headache improved in two hours period. During this period the patient became agitated and anxious. Therefore, iv diazepam was applied to the patient and simultaneous termination of headache and conversion to sinus rhythm was observed in a few minutes (**Figure 2**). The patient was observed in the coronary intensive care unit for 24 hours and discharged from the hospital with beta blocker treatment in sinus rhythm and neurologically stable condition. Written informed consent was obtained from the patient.

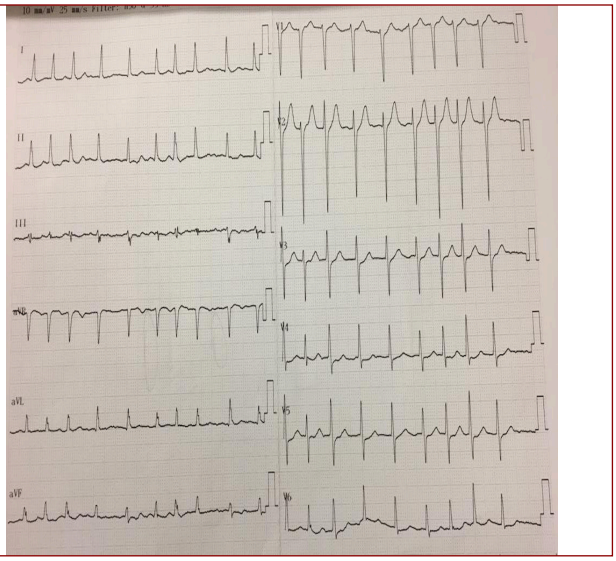

Figure 1. Admission 12-lead electrocardiography of the patient consistent with atrial fibrillation with high ventricular rate.

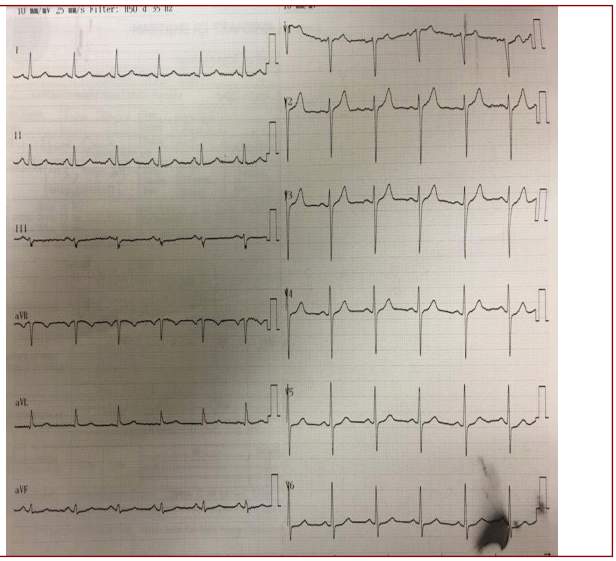

Figure 2. 12-lead electrocardiography of the patient consistent with sinus rhythm simultaneous with the termination of migraine headache after benzodiazepine treatment.

DISCUSSION

We present the case of a young patient with simultaneous acute migraine headache and AF attack and successful treatment of both conditions simultaneously with iv administration of BZD. To our knowledge, this is the first case in the literature demonstrating beneficial effect of BZD in acute migraine headache and accompanying AF. Although there is a close association between migraine and AF, pathophysiological mechanisms and clinical significance of this relationship are not entirely known.4 In addition, there are relatively few reports documenting the occurrence of AF during migraine headache.[2,5]

Besides being a significant cause of debilitating symptoms and disability especially among young individuals, migraine headache is also linked with ischemic vascular pathologies including stroke and coronary heart disease. It is primarily defined as a neurological disease with various symptoms and manifestations affecting the peripheral organs associated with gastrointestinal system, central nervous system, heart, and circulation. Nausea, vomiting, diarrhea, anorexia, pallor, flushing, piloerection, diaphoresis and mood disturbances are the main symptoms accompanying migraine headache and autonomic dysfunction, which occurs as a result of an imbalance between the sympathetic and parasympathetic system, underlies the pathogenesis of the disease and the occurrence of these symptoms.[1,7] For instance, sympathetic hyperactivation and a concomitant decrease in parasympathetic functions were demonstrated previously in migraineurs.[8] In a similar manner, sympathetic system activation during migraine attack may be the underlying mechanism triggering AF in our patient. However, iv administration of metoprolol, an agent that inhibits the sympathetic nervous system activation centrally, did not terminate the attacks. Furthermore, it is not possible to directly conclude that AF is secondary to migraine headache in this patient although syncope episode occurred after the initiation of headache. Nonetheless, concurrent termination of headache and AF highlights a robust pathophysiological connection between acute migraine headache and AF attack in this patient.

AF is the most common arrythmia all over the world and associated with excess risk of morbidity and mortality. Stroke is the most devastating complication of AF, and its frequency also increases in migraine patients. Alterations in the functioning of autonomic nervous system is known to play role in the pathophysiology of AF akin to the migraine.[7] Increasing line of evidence suggests that atrial repolarization abnormalities contribute to the initiation and maintenance of AF in migraineurs.[3,7] Moreover, atrial conduction abnormalities and diastolic dysfunction, which are contributors of AF development, were shown in migraineurs in previous transthoracic echocardiography studies.[9,10] Furthermore, presence of diastolic dysfunction was linked with a long migraine history.[10] When it comes to our patient, there was a slightly increased left atrium diameter that could make the patient prone to AF development. Otherwise, he had no history and/or signs of vascular disease, hypertension, diabetes mellitus, stroke, and heart failure. Accordingly, the patient was not anticoagulated and was planned to be followed up with beta blocker treatment. Subsequent examinations including stress test and ambulatory rhythm monitoring were planned to be performed during outpatient visits according to the clinical status and complaints of the patient.

BZDs modulate the effect of inhibitory neurotransmitter GABA through GABA-A receptors in the central nervous

system. In general, GABA plays an inhibitory role in the brain by reducing neuronal excitability and transmission. This inhibitory activity underpins anxiolytic, anticonvulsant, sedative-hypnotic and muscle relaxant effects from a clinical perspective.[6] In our case, we decided to use BZD in order to relief the patients' anxiety and agitation, but BZD did not only improve anxiety but also terminated AF and migraine headache simultaneously. In their case series, Kahn et al. demonstrated that clonazepam, which is a highly potent BZD, improved AF episodes in some patients suffering from panic disorder.[11] To our knowledge, concurrent improvement in AF and migraine attack has not been demonstrated in the literature hitherto.

It is reasonable to ask how BZD administration achieved this therapeutic effect. Neurobiological mechanisms and pathways of this effect might be multifactorial and complex. Basically, relief of anxiety and agitation might have alleviated the attacks through GABAergic stimulation subsequently inhibiting sympathetic nervous system activity. For example, according to a recent clinical study GABA containing tea significantly decreased immediate stress score and improved heart rate variability among university students.[12] In a similar manner, central GABA-A receptor activation were shown to decrease blood pressure and heart rate in an animal model study.[13] On the contrary, microinjections of GABA or its receptor agonist into the intermediate nucleus tractus solitarii of anaesthetized animals produced hypertension and tachycardia according to a previous study.[14] When it comes to effects of BZDs in migraine, treatment with short-acting BZDs but not long-acting ones was associated with migraine occurrence through one year follow-up period.[15] On the other hand, beneficial effects of lorazepam, a subtype of BZD, was shown to be beneficial in alleviating the symptoms of acute migraine headache.[16]

CONCLUSION

It is not logical to conclude that BZDs can be used in the treatment of AF and/or migraine headache in the light of this case report. However, this mutual effect deserves to be investigated in future studies and might open a new avenue in pharmaceutical investigations of both diseases. In conclusion, simultaneous initiation of acute migraine headache and AF attack and concurrent termination of both conditions after BZD therapy is an interesting situation that needs to be investigated in well-designed preclinical and clinical studies. Close follow-up of this patient might give important clues about the pathophysiology of migraine and AF.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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